PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
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PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing *(day/month/year)*	17 FEB 2005

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
3268.1003003	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US03/36975	19 November 2003 (19.11.2003)	20 November 2002 (20.11.2002)

Applicant

NORTH SHORE-LONG ISLAND JEWISH RESEARCH INSTITUTE

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US	Authorized officer
Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450	David J. Blanchard Telephone No. (571) 272-1600
Facsimile No. (703)305-3230	

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 3268.1003003	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US03/36975	International filing date *(day/month/year)* 19 November 2003 (19.11.2003)	Priority date *(day/month/year)* 20 November 2002 (20.11.2002)
International Patent Classification (IPC) or national classification and IPC IPC(7): C07K 5/00, 16/00; A61K 39/395; C12N 15/00 and US Cl.: 530/350, 387.3, 388.8; 424/134.1, 155.1; 435/69.7		
Applicant NORTH SHORE-LONG ISLAND JEWISH RESEARCH INSTITUTE		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of ___ sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01 June 2004 (01.06.2004)	05 January 2005 (05.01.2005)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer David J Blanchard Telephone No. (571)272-1600

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PR[redacted]MINARY EXAMINATION REPORT

Internation[redacted]ication No.
PCT/US03/[redacted]

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed.

☒ the description:
pages 1-35 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 36-40, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages 1-13, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the sequence listing part of the description:
pages 1-14, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☒ contained in the international application in printed form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*
*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International Application No.
PCT/US03/[redacted]

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	6-45.	YES
	Claims	1-5.	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-45.	NO
Industrial Applicability (IA)	Claims	1-45.	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS
Please See Continuation Sheet

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International [redacted]ation No.
PCT/US03/36[redacted]

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Krieg et al teach immunostimulatory nucleic acid molecules comprising unmethylated CpG sequences for treating, preventing or ameliorating a tumor or cancer, a viral, a fungal, a bacterial or parasitic infection in an individual and can be administered in conjunction with a vaccine (see columns 6 and 33). Krieg et al teach that unmethylated CpG containing nucleic acid molecules preferentially activate monocytic cells such as dendritic cells as well as NK cells (see column 13, lines 11-15) and induced spleen cells to secrete numerous cytokines including IL-3 and IL-12 (see column 33, lines 22-26). Krieg et al teach that for many pathogens, the humoral response contributes little to protection, and can even be detrimental" (see column 33, lines 56-61). Further, Krieg et al teach that unmethylated CpG nucleic acids induce Th1 type cytokines (IL-12 and IFN-gamma) and shift the immune response in a subject from a Th2 to a Th1 response.
Lode et al teach that targeting of cytokines into the tumor microenvironment using antibody-cytokine fusion proteins is highly effective in boosting cancer vaccines (see entire document).
Johnson D. A. teach pharmaceutical compositions and vaccine compositions that are effective to potentiate an immune response to one or more antigens, wherein the antigen is a tumor associated antigen (tumor specific antigen) (see columns 32-33). Johnson D. A. teach adjuvants for eliciting a predominantly Th-1 type response including monophosphoryl lipid A and CpG oligonucleotides.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a pharmaceutical composition comprising an HMGB1 B box polypeptide for inducing an immune response and for treating cancer in an individual and to attach the HMGB1 B box polypeptide to an antibody that binds a tumor-associated antigen for therapeutic benefit of cancer in view of Wen et al and Andersson et al and Krieg et al and Lode et al and Johnson D. A because Wen et al teach the human HMG-1 polypeptide, which inherently comprises an HMGB B box and Andersson et al teach that HMG-1 acts as a cytokine that specifically stimulates cytokine synthesis in human monocytes and HMG-1 significantly increases cellular uptake of DNA and Krieg et al teach DNA (immunostimulatory nucleic acids) comprising unmethylated CpG sequences for treating, preventing or ameliorating a tumor or cancer and can be administered in conjunction with a vaccine and Lode et al teach that targeting of cytokines into the tumor microenvironment using antibody-cytokine fusion proteins is highly effective in boosting cancer vaccines and Johnson teach pharmaceutical compositions and vaccine compositions comprising Th-1 type adjuvants (i.e., monophosphoryl lipid A and CpG oligonucleotides) that are effective in potentiating an immune response to one or more antigens, wherein the antigen is a tumor associated antigen. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have prepared a pharmaceutical composition comprising the HMG-1 polypeptide taught by Wen et al and a CpG oligonucleotide for inducing an immune response in a patient and for treating cancer in a patient and it would have been obvious to one of ordinary skill in the art to have attached the HMG-1 polypeptide to an antibody for targeting the HMG-1 polypeptide (cytokine) into the tumor microenvironment, to more effectively boost a cancer vaccine as taught by Lode et al.

Claims 1-45 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

----------NEW CITATIONS----------
U.S. 6,207,646 B1 (KREIG et al) 27 March 2001 (27.03.2001), see entire document, especially columns 6, 11 and 33.